

addition, claims 1 and 9 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Koster, in view of Richards and further in view of Wu (*Genomics* 1989, Vol. 4, pp. 560-569).

The title of the application is herein amended to "Primers Useful for Sizing Nucleic Acids." As requested in the Office Action, the title is amended for clarity. Applicants respectfully request that the objection to the title be withdrawn.

#### THE CLAIMS ARE NOT OBVIOUS

The rejection also alleged that the claims are obvious over Koster in view of Richards or over Koster in view of Richards and Wu under 35 U.S.C. § 103(a). Applicants respectfully traverse.

Three requirements must be met for a prima facie case of obviousness. First, the prior art references must teach all of the limitations of the claims. M.P.E.P. § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must both be found in the prior art and not based on Applicant's disclosure. M.P.E.P. § 2143.

#### *The cited references do not teach every element of the claimed invention*

The present invention provides, e.g., nucleic acid primers for use in sizing nucleic acids, e.g., using mass spectrometry. The nucleic acids primers of the invention comprise a 5'-region and a 3'-region. The 5'-region comprises an immobilization attachment site and the 3'-region comprises a cleavable site and is extendable by an enzyme, e.g., to produce PCR extension products. The extension products are then typically cleaved at the 3'-primer site to remove most of the primer sequence prior to analysis.

Koster allegedly teaches mass spectrometry of nucleic acids that have been extended using PCR. In addition, the nucleic acids of Koster allegedly comprise 5'-immobilization sites for attaching the nucleic acids to a solid support. However, as the Office Action points out, Koster does not teach a cleavable site in the 3'-region of a PCR primer. Richards allegedly teaches modification of a nucleic acid, e.g., to produce a cleavable site, e.g., in a primer, and Wu allegedly teaches the use of a ligase in an amplification reaction.

*not in the claim*

The references cited do not teach every element of the claims because, among other things, they do not teach a cleavable site in a 3'-region of a primer or any reason why such an approach might be desirable. If anything, Richards teaches modification of nucleic acids and nucleic acid primers. Nothing in Richards teaches the specific modification of a 3'-region of a primer, e.g., to aid in removal of the primer prior to analysis. *not in claim* In the present invention, the 3'-position of the cleavable site is important, e.g., for removing the majority of nucleotides in the primer prior to analysis. The cited references do not mention modification of the 3'-region of a primer. Therefore, the cited references do not teach every element of the claimed invention.

*not*

In addition, Applicants respectfully point out that the claimed invention as a whole must be considered when determining obviousness. M.P.E.P. § 2142.02. When considering the claimed invention as a whole, it is clear that a cleavable site in the 3'-region of a primer, e.g., to reduce the length of the nucleic acid prior to analysis, must be taught in the prior art to make the claimed invention obvious. Neither Koster, Richards, or Wu teaches a 3'-cleavable site in a nucleic acid primer. In addition, none of the references teach the utility of reducing the mass or length of nucleic acids prior to analysis. In the present invention, the primers are typically removed prior to analysis to increase the efficiency of mass spectrometry in sizing nucleic acids. *not in the claim* For example, the primer sequence and size are typically known and therefore, no need exists to include it in the sizing analysis. The primer in the present invention is therefore altered to include a cleavable site in the 3'-region to remove the majority of the primer sequence prior to analysis. For example, typically five or fewer of the primer nucleotides remain in a nucleic acid after cleavage at the 3'-site. The cited references do not teach a 3'-cleavable site in a nucleic acid primer or the utility of reducing the length of a nucleic acid prior to analysis, and therefore, do not teach every element of the invention.

*No motivation existed to combine the cited references*

The critical inquiry in determining motivation to combine is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness of making the combination. *See, In re Nowell*, 13 U.S.P.Q. 1248, 1250 (Fed. Cir. 1989). No motivation existed at the time of filing the present application to modify the nucleic acids of Koster using the methods of Richards.

No motivation existed to combine the Koster reference, which allegedly teaches nucleic acid primers comprising 5'-region immobilization sites, with Richards, which teaches reduction of contamination in nucleic acid amplifications, e.g., using modified nucleotides, to create the nucleic acid primers of the present invention. The present invention comprises a 3'-cleavage site in a primer, which site is selectively cleaved prior to nucleic acid sizing, thereby reducing the length of the nucleic acid of interest such that it typically contains about 5 or fewer nucleotides from the primer sequence. The reduction in length of the nucleic acid of interest increases the efficiency of mass spectrometry analysis by avoiding analysis of known sections of the nucleic acid. No motivation existed, outside Applicants' disclosure, to reduce the length of a nucleic acid prior to analysis, e.g., by cleaving at a 3'-primer cleavage site, e.g., to detect nucleic acid polymorphisms by mass spectrometry.

The Office Action alleged that Koster teaches cleavable sites, but not in the 3'-region of the primer, and that Richards teaches modification of an amplified product by incorporating a modified base into the primer prior to amplification. The Action further alleged that the combination of these two references produces the primers of the present invention. It is unclear what motivation existed to combine these references or what primer would result from such a combination. Assuming, arguendo, that the references teach what the Office Action alleged, the resulting primer would have a 5'-immobilization site and modified nucleotide. However, the modified nucleotide would not necessarily be in the 3'-region, since neither reference specifically mentions the 3'-region of the primer. Therefore, the modification of Koster, by Richards or by Richards and Wu, would not produce the claimed invention.

Furthermore, when considering the presently claimed invention as a whole, it is clear that reduction in length of a nucleic acid prior to analysis must be taught in the prior art to make the claimed invention obvious. Koster does not teach or suggest reduction in length of nucleic acids; and even assuming, arguendo, that Richards teaches methods of modifying primers, neither provides a reason to incorporate a cleavage site into a 3'-region of a primer to determine the mass of the nucleic acid. Therefore, no motivation to combine these references is found in the prior art. Nor has the Office action articulated any motivation for the alleged combination which is found in the prior art.

In fact, the references teach away from the present invention. For example, Koster teaches increasing the mass or length of a nucleic acid prior to sequencing. *See, e.g.*, the abstract. Richards teaches modification of a nucleotide in a primer in order to incorporate a corresponding modification into an amplified product. The primer modification in Richards is not used as a cleavage site because the primer modification produces a desired modification in the amplified product. Therefore, Richards also teaches away from cleavage at the modification site. In the present invention, the cleavable site is in the 3'-region to facilitate cleavage of a known primer sequence which is unnecessary to future analysis. The fact that prior art contains negative teachings that would have discouraged and deterred a person of skill in the art from making the invention at issue is further evidence of non-obviousness. *See, e.g.*, M.P.E.P. § 2142.02. As no motivation to combine Koster and Richards existed outside of Applicants' disclosure and the references teach away from such a combination, the present claims are not obvious over Koster in view of Richards or in view of Richards and Wu.

*No expectation of success existed for the claimed invention based on the prior art*

Before an invention can be considered obvious, it must be shown, without resorting to Applicants' disclosure, that the prior art motivates the invention and that one of skill would have had a reasonable expectation that the invention would be successful. The Office Action did not establish why one of skill would have expected a successful or improved nucleic acid primer based on a combination of Koster and Richards.

The prior art provides no motivation to practice the present invention as claimed or no expectation that it would have worked. The prior art used primer modification to increase the length and/or size of nucleic acids or to incorporate modifications into the amplified product, therefore, no expectation existed in the prior art that 3'-cleavable sites in primers would lead to an improved method of nucleic acid analysis.

The claims are not obvious over the cited references because they do not teach every element of the claims and no motivation existed to combine the references. Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

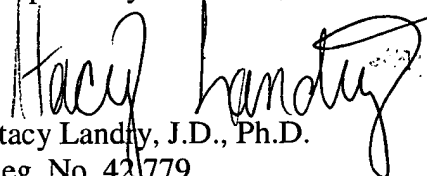
The cited art does not provide the elements of the claimed invention, and no motivation existed to combine the references to provide the present invention. Therefore, obviousness has not been established and Applicants respectfully request that the rejections for alleged obviousness be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. In the event that any substantive issues remain, Applicants formally request an Examiner interview prior to issuance of any new office action.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 510-337-7871.

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